EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 14 April 2021

Addressees
Registrant of Propane-1,3-diyl dioctanoate as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
20/11/2013

Registered substance subject to this decision ("the Substance")
Substance name: Propane-1,3-diyl dioctanoate
EC number: 700-003-3
CAS number: 56519-71-2

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***21 July 2022***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: OECD TG 210)

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII and VIII to REACH, for registration at [redacted] tpa;

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification

and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided the following information:

- a short-term toxicity study on aquatic invertebrates performed on the Substance (according to OECD TG 202, [redacted] 2009) but no information on long-term toxicity on aquatic invertebrates for the Substance.

We have assessed this information and identified the following issues:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

In you dossier the saturation concentration of the Substance in water was determined to be below 0.01 mg/L.

Therefore, the Substance is poorly water soluble and information on the long-term toxicity on aquatic invertebrates must be provided.

In your comments on the draft decision you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, section 1.5 of the REACH Regulation.

You propose to predict the properties of the Substance for long-term toxicity on aquatic invertebrates from source studies yet to be conducted on the analogue substance CAS 68583-51-7, which have been requested by ECHA in a separate compliance check decision.

You have provided the following reasoning for the prediction of ecotoxicological properties. You claim that the two substances are similar and some studies conducted on substance CAS 68583-51-7 are already included in the dossier of the Substance and this read-across approach has been validated by ECHA. You also indicate that you will update the justification of your read-across strategy.

We have assessed this information and identified the following issues:

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).
A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on

recognition of the structural similarities and differences between the substances[2]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the structural similarity between the source substance and your Substance is a sufficient basis for predicting the properties of your Substance.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar ecotoxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a ecotoxicological property, based on recognition of the structural similarities and differences between the source substance and your Substance.

Furthermore, while ECHA acknowledges that the read-across adaptation using data with CAS 68583-51-7 as a source substance has been accepted to fulfil the standard information requirement for the endpoint eye irritation (Annex VII, 8.2.), ECHA notes that read-across is endpoint specific and acceptable read-across adaptation in one endpoint does not automatically mean that such read-across can be used to fulfil some other endpoint.

As your strategy relies on a read-across hypothesis and on supporting information that needs to be fully described and justified, as well as on data which is yet to be generated, no assessment or conclusions on the compliance can currently be made. Should you decide to pursue the strategy presented in your comments, ECHA will assess its compliance in the follow-up to the dossier evaluation.

Study design

The Substance is difficult to test due to the low water solubility (below 0.01 mg/L). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solutions.

[2] *Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals.*

Appendix B: Reasons to request information required under Annex VIII of REACH

1. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have provided an adaptation under Annex VIII, Section 9.1.3., Column 2 with the following justification *"the study for acute toxicity to fish does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur. Such mitigating factors may be that test substance is highly insoluble in water or it is too large to cross biological membranes. The water solubility of propanediol dicaprylate was determined to be less than 0.01 mg/L."*

You have provided no information on long-term toxicity on fish for the Substance.

We have assessed this information and identified the following issue:

A. Under Section 9.1.3., Column 2, first indent, Annex VIII to REACH, the short-term fish study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. ECHA Guidance R.7.8.5 explains that there is no scientific basis to define a cut off limit for solubility below which toxicity is unlikely. Therefore, the justification must demonstrate very low water solubility and low likelihood to cross biological membranes. For the latter, the indicators used for low likelihood of uptake (ECHA Guidance R.11, Figure R.11-4) must be considered, including:
   - physico-chemical indicators of hindered uptake due to large molecular size (*e.g.* D_{max} > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (log K_{ow} > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and
   - supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

   Unless it can reliably be demonstrated that aquatic toxicity is unlikely to occur, the Substance must be considered as poorly water soluble.

   Your registration dossier provides:
   - information on the solubility of the Substance in water below 0.01 mg/L based on OECD TG 105.
   - a conclusion of low likelihood to cross biological membranes based on hindered uptake of the Substance without substantiation.

   Even though the water solubility of the Substance is low, the following does not support your justification:
   - based on the information in the dossier the physico-chemical indicators do not support your conclusion of low likelihood to cross biological membranes because the log Kow is below 10 (Log Kow = 7.6) and MW is below 1100 (MW = 328.48).
   - you do not provide any other supporting experimental evidence of hindered uptake.

   Therefore, you have not demonstrated that toxicity is unlikely to occur and your adaptation is rejected and the Substance must be considered as poorly water soluble.

B. Poorly water soluble substances require longer time to reach steady-state conditions. As

a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

As already explained under Section A.1, the Substance is poorly water soluble and therefore, information on long-term toxicity on fish must be provided, irrespective of the validity of your adaptation under Section 9.1.3., Column 2, first indent, Annex VIII to REACH.

In your comments on the draft decision you indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, section 1.5 of the REACH Regulation.

You propose to predict the long-term toxicity on fish properties of the Substance from studies yet to be conducted on substance CAS 68583-51-7, which have been requested by ECHA in separate compliance check decision.

You have provided the following reasoning for the prediction of ecotoxicological properties. You claim that the two substances are similar and some studies conducted on substance CAS 68583-51-7 are already included in the dossier of the Substance and this read-across approach has been validated by ECHA. You also indicate that you will update the justification of your read-across strategy.

We have assessed this information and identified the following issues:

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances[3]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the structural similarity between the source substance and your Substance is a sufficient basis for predicting the properties of your Substance.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar ecotoxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a ecotoxicological property, based on recognition of the structural similarities and differences between the source substance and your Substance. Furthermore, while ECHA acknowledges that the read-across adaptation using data with CAS 68583-51-7 as a source substance has been accepted to fulfil the standard information requirement for the endpoint eye irritation (Annex VII, 8.2.), ECHA notes that read-across is endpoint specific and acceptable read-

[3] *Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals.*

across adaptation in one endpoint does not automatically mean that such read-across can be used to fulfil some other endpoint.

As your strategy relies on a read-across hypothesis and on supporting information that needs to be fully described and justified, as well as on data which is yet to be generated, no assessment or conclusions on the compliance can currently be made. Should you decide to pursue the strategy presented in your comments, ECHA will assess the compliance in the follow-up to the dossier evaluation.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[4].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix D: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 16 April 2020.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s), but amended the deadline.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 12 months from the date of adoption of the decision.

In your comments to the draft decision you requested ECHA to extend the standard granted time to a total of 15 months based on the additional time required to align with the comments of the draft decision concerning analogue substance CAS 68583-51-7, to allow time for the coordination by the registrants of the category, and to develop the suitable analytical methods.

ECHA took this information into account and granted 3 months extension to the original deadline for development of analytical methods and preparation of test solutions. Therefore, the deadline is set to 15 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[8]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.